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The objective of the project is to test whether the therapeutic effectiveness of permanent implant brachytherapy for prostate cancer can be improved by using a combination of short and long half life radionuclides simultaneously. A theoretical model for continuous low dose rate irradiation using a mixture of radionuclides has been developed. Experiments have been performed using BA1112 tumor cells and Chinese Hamster cells growing in vitro and BA1112 cells growing in vivo as solid tumors in WAG/rij rats. Radiobiology parameters for these cells have been determined and used in the theoretical radiobiology model to improve our understanding of the experimental observations. We have designed and fabricated applicators for in vivo irradiations as well as developed the animal care procedures. We have performed in vivo experiments for tumor growth studies using the BA1112 rat model with ^{125}I seed applicators. Further experiments with ^{103}Pd and mixed radionuclides are in progress. The in vivo studies with the rat model have been very difficult to perform because of the nature of these brachytherapy experiments, which involve long irradiation times. We would focus on completing the studies using the rat model in the next year.

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INTRODUCTION

The objective of the project is to test whether the therapeutic effectiveness of permanent implant brachytherapy for prostate cancer can be improved by using a combination of short and long half life radionuclides simultaneously. Specific aims of the proposed project are:

1. To test theoretically the potential of a mixture of radionuclides in permanent implants, using the linear quadratic model, as a function of T_{pot}, potential tumor doubling time.

2. To test experimentally the validity of this concept by in vitro irradiation of BA1112 sarcoma cells at a continuous low dose rate (CLDR) with ^{125}I (60 d half life), ^{103}Pd (17 d half life) and a 50:50 mixture of ^{125}I and ^{103}Pd under aerobic conditions leading to exponential growth at different rates (from near quiescence to full exponential growth at a maximal rate, with a doubling time of approximately 14 hours).

3. To measure the radiobiology parameters such as alpha, beta, half life of repair for the BA1112 sarcoma cells under different growth conditions and develop a theoretical model to predict expected levels of cell killing using ^{125}I, ^{103}Pd or a mixture of these isotopes.

4. To use immunohistochemical techniques to measure, in solid BA1112 tumors in vivo, the proportion of cells in S phase, the proportion proliferating and non-proliferating cells and the tumor doubling time.

5. To test the therapeutic effectiveness of ^{103}Pd, ^{125}I and a Pd/I mixture in the BA1112 in vivo tumor system;

6. To test the therapeutic effectiveness of ^{103}Pd, ^{125}I and a Pd/I mixture in human prostate carcinoma xenografts in nude mice, using a slow growing and a fast growing carcinoma.

7. To evaluate the clinical potential and feasibility of this approach in the treatment of human prostate cancer.

BODY OF THE REPORT

We have developed a theoretical radiobiology model for cell-killing by continuous low dose rate irradiation (CLDRI) using a mixture of radionuclides. Theoretical studies were performed to investigate the hypothesis and to plan in vitro and animal studies. Experiments have been performed using BA1112 tumor cells and Chinese Hamster cells growing in vitro and BA1112 cells growing in vivo as solid tumors in WAG/rij rats. Radiobiology parameters for these cells have been determined and used in the theoretical radiobiology model to improve our understanding of the experimental observations.

The linear-quadratic model of cell-killing by CLDRI Using a Mixture of Radionuclides

We have developed a theoretical model for CLDRI using a mixture of radionuclides with different half lives. This model is described in the attached manuscript entitled "Biologically effective dose (BED) for interstitial seed implants containing a mixture of radio-nuclides with different half lives" by Zhe Chen and Ravinder Nath. Briefly, the purpose of this project was to develop a tool for evaluating interstitial seed implants that contain a mixture of radionuclides with different half-lives and to examine the clinical implications of prescribing to an isodose surface for such an implant. Using a generalized equation for the biological effective dose (BED)[1-4], the effects of cell proliferation and sub-lethal damage repair were examined systematically for implants containing a mixture of radionuclides (Figure 1). The results were contrasted with those for implants using a single type of radionuclide. A clinical permanent seed implant that contained a mixture of ^{125}I and ^{103}Pd seeds was used to examine the clinical implications of the isodose prescription for such implants. An equation of BED for implants containing any number of radionuclide types was obtained. For implants containing a mixture of radionuclides with different half-lives such as ^{125}I and ^{103}Pd, the dose as well as its temporal delivery pattern to a point is dependent on the relative dose contributions from different types of radionuclide. It can vary from point to point throughout the implant volume. Therefore the quantitative effects of cell proliferation and sub-lethal damage repair are spatially dependent in such an implant. For implants containing a mixture of ^{125}I and ^{103}Pd seeds, the prescription to an isodose surface becomes non-unique. If the prescription dose was based on existing clinical experience of using ^{125}I seeds alone, mixing ^{103}Pd seeds with ^{125}I seeds would decrease the cell survival in such implant. On the other hand, if the prescription dose was based on existing clinical experience of using ^{103}Pd seeds alone, mixing ^{125}I seeds with ^{103}Pd seeds in a same implant would create radiobiologically "cold" spots (i.e. an increase in cell survival from the clinical expectation) at locations where a major portion of prescription dose is contributed by the ^{125}I seeds. For fast-growing tumors, these "cold" spots can become significant. From this theoretical investigation, we conclude that when

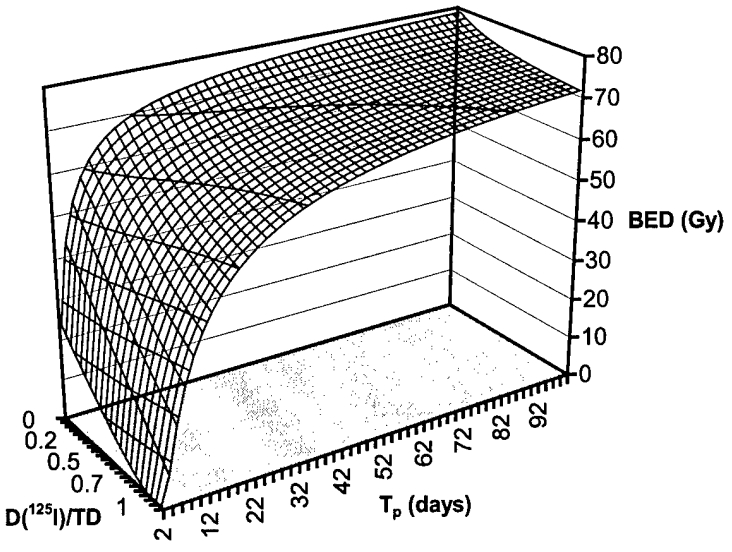

Figure 1

cell proliferation and sub-lethal damage repair are present during dose delivery, total dose alone is no longer sufficient for a complete characterization of an interstitial seed implant. In order to avoid radiobiological "cold" spots when radionuclides of different half-lives are mixed in a permanent implant, the dose prescription should be based on the clinical experience of using the longer half-life radionuclide. Biologically effective dose provides a tool to start examining the radiobiological effects of mixing different type of radionuclides in the same implant.

A manuscript has been submitted for publication in the International Journal of Radiation Oncology.

In vitro CLDRI studies

BA1112 tumors were grown between the ears of the a 14 week old male WAG/rij rats by interdermal inoculation from a single cell suspension of BA1112 cells obtained from a 21 day BA1112 tumor growing on the head of a previously inoculated rat. A tumor cell suspension was made from the BA1112 tumor and between $1.5x10^5$ and $5.0x10^5$ cells were plated into petri dishes. These cells were allowed to settle and reach logarithmic growth, (48-72 hrs), before they were used in a continuous low dose rate experiment.

Monolayers of rat rhabdomyosarcoma cells (BA1112) were irradiated in vitro by ^{103}Pd sources in a polystyrene phantom. Colony formation ability of irradiated cells under aerobic conditions was measured for graded doses, at a dose rate of 6 cGy/hr. Dose to the cell monolayers was determined using $FeSO_4$ Fricke dosimetry, with a calculated correction for interface effects due to photoelectric effect in the tissue culture dishes. The sources (up to 60 in one experiment) were arranged in concentric circles in such a way as to provide a dose uniformity of better than ± 5% across the dishes. Some of the results are shown in Figure 2. Comparison of the surviving fraction as a function of dose calculated for the BA1112 cells to that measured by using CLDRI ^{103}Pd irradiation is also shown in Figure 2. The lines through the data points represent the calculated survival curves the symbols represent the measured data The parameters of α, β, repair half-time, and tumor doubling time were determined directly from the measurements performed on the BA1112 cells, as described later in the report.

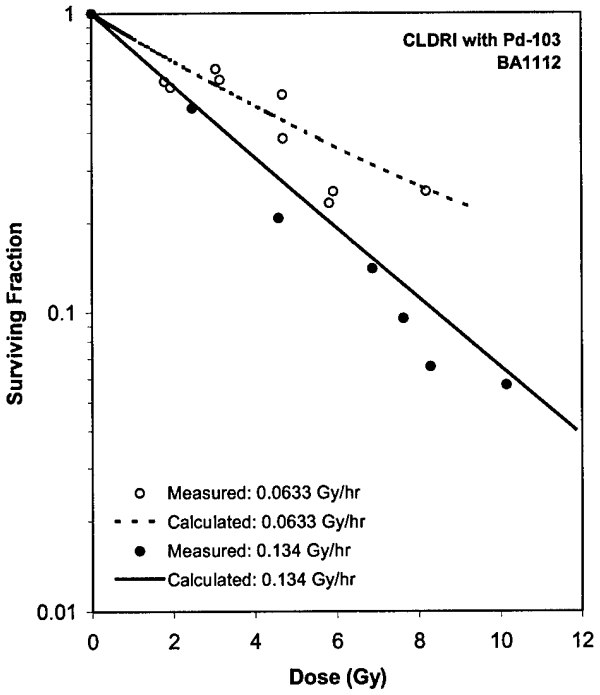

Figure 2.

In vitro studies at an acute dose rate using simulated x-ray beams

To study the radiobiological characteristics of the cells under acute exposure condition, simulated x-ray beams with average energies equivalent to that emitted by ^{125}I (27.2 – 35.49 keV with an average of 27.4) and ^{103}Pd (20 – 22.7 keV with an average of 20.5 keV) were established on a new orthovoltage unit. The simulated beams not only have the average energies similar to that given by the radioactive isotopes but also have a narrow photon energy spectrum. The narrow photon energy spectrum was achieved by optimizing the tube voltage (which determines the upper limit of the produced photon energy) and the added filtration (which filters out the low-energy Bremsstrahlung photons), following the work of Muench et al[5].

Aluminum filters from Pantak was used to construct a customized filter for the DXT 300 unit that has a desired filtration thickness. A set of aluminum filters (with thickness of 0.1 to 1.0 mm) from Nuclear Associates (AL Filter Set 07-430) were used to determining the half-value-layer (HVL) of a simulated beam using a customized filtration. The thickness of the aluminum sheets were measured by using a Mitutogo micrometer (Serial # 2032360) with accuracy of 0.001 mm). The aluminum HVL for a given beam was determined by in-air ionization chamber measurement under the narrow beam geometry. An air-equivalent Spokas chamber (Exradin, Model No: A1 (0.5 ml, AE plastic)) was used to measure the ionization at a fixed source to chamber distance (SCD) of 50 cm in air. The ionization charge was measured by a Keithley electrometer (model 35614E SN 43075) with –300 V bias potential. Due the energy dependence of the chamber at the low energies, the measured ionization were converted to corresponding exposure and the HVL is then determined from the relative exposure as a function of aluminum filter thickness. A narrow circular beam, with a diameter of 6 cm at SCD of 50 cm, was generated by using a homemade lead collimator mounted to DXT 300's accessory mount. The aluminum sheets added to the beam for the HVL measurement were taped to the bottom of the lead collimator.

The HVL as a function of mono-energetic photon beam energy for aluminum is taken from Johns and Cunningham[6]. The expected HVL for a simulated ^{125}I (^{103}Pd) beam with average energy of 27.4 keV (20.5 keV) is 1.84 mm (0.82 mm) aluminum. With the expected HVL in mind, the tube kV, mA and the thickness of the added filtration were optimized for a simulated ^{125}I and a simulated ^{103}Pd x-ray beam. The optimum setting determined for the DXT 300 unit is summarized in the following table I.

Table I. Radiation characteristics of simulated x-ray beams

Beam	kV	mA	Added Filter (mm AL)	Beam HVL (mm AL)	Energy Homogeneity (%)	Equivalent Energy (keV)	<E> from isotope (keV)
I-125 Equivalent	43	20	3.545	1.851	86.9	27.45	27.4
Pd-103 Equivalent	29	25	1.826	0.82	88.6	20.5	20.5

Results of the cell survival experiments at an acute dose rate using these x-ray beams are shown in Figure 3 and 4. The parameters of α, β, repair half-time, and tumor

doubling time were determined directly from the measurements performed on the BA1112 cells (details are provided separately).

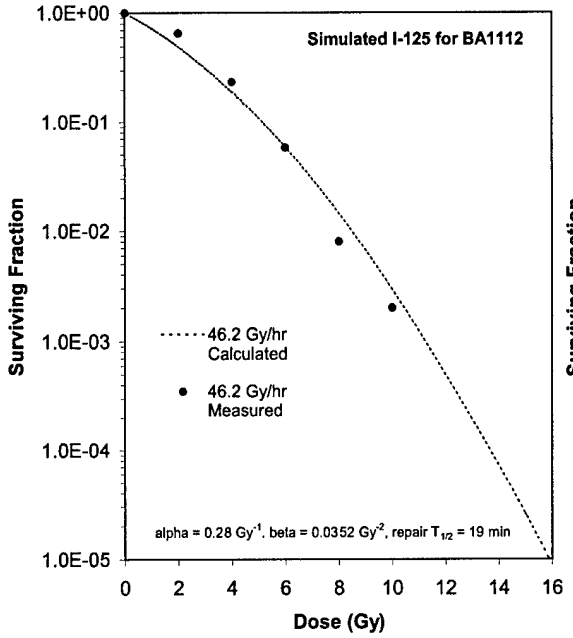

Figure 3. Comparison of the surviving fraction as a function of dose calculated for the BA1112 cells to that measured using the simulated ^{125}I x-ray beams.

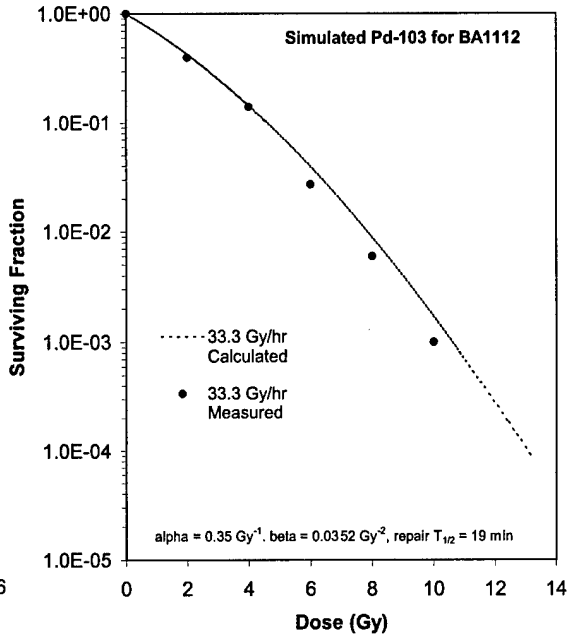

Figure 4. Comparison of the surviving fraction as a function of dose calculated for the BA1112 cells to that measured using the simulated ^{103}Pd x-ray beams.

Procedure for in vitro studies for quiescent BA1112 cells

A procedure for in vitro studies for quiescent BA1112 cells has been developed. For these studies, animals will be implanted with transplanted BA1112 rhabdomyosarcomas by inoculation, into a subcutaneous site on the heads. The tumors will be allowed to grow for 3 weeks, to an experimental volume of approximately 100-200mm^3. The animals chosen for the quiescent cell experiments will be euthanized by anesthetic overdose and the tumor cells will then be removed using aseptic techniques. A single-cell suspension of tumor cells will be suspended, counted, and assayed for viability using the same colony formation assay used for cells in cultures. 1.5 x10^5 cells will be plated into a flask with 13 ml of DMEM for cell growth. These cells will then be passed twice a week for approximately 4-8 passages. The cells are transplanted for 2-4 weeks to assure a homogeneity population of BA1112 cells. After 8-10 passages of the BA1112 cells, in vitro, a new in vivo tumor is used to produce a new primary single-cell passage, as described above.

When the first line has reached passage 5 the cells are counted and plated into 5 petri dishes for a growth curve study. 1.0 x10^5 cells/dish are planted on Day 0. The cells are allowed to grow for 24 hours and cell counts are taken on days 3-7. Our first cell count reading is taken 24 hours after initial seeding. This is to assure lag phase has occurred

and the cells are in exponential growth. Within this one week exponential cell growth occurs, and a population of $3.6x10^6$ cells/dish accumulates by Day 6. Plateau phase is reached by Day 7 ($3.1x10^6$ cells/dish). An in vitro growth curve is plotted to assure the primary tumor cells have adjusted to their in vitro environment. Their doubling times are approximately 24 hours.

In our initial experiment, the exact cell number per dish was repeated as in the previous experiment with the addition of 5 dishes (media-change dishes). The media in these dishes are changed every 24 hours, to accelerate cell division and to reach quiescent growth more quickly. Upon completion of this experiment, the control dishes (media not changed), showed similar results as the control experimental dishes, but the experimental dishes (media replaced) had a dramatically higher cell counts and did not seem to reach a plateau phase. The experimental dishes reached $1.1x10^7$ cells/dish and Day 7, and were not growing exponentially as in Days 3-5, but were in a quiescent phase, still alive and not dividing.

In our third experiment, cells were plated similarly as the previous experiment but the initial seeding of the dishes was increased to 10^6 cells/dish. Our results showed the control dishes seeded with 10^6 cells/dish and no media changes, throughout, reached plateau by Day 5 and the quiescent phase was probably attained by late Day 3-4. The experimental dishes, seeded with 10^6 cells/dish also, and the media replaced every 24 hours, showed early plateau phase on Day 7. Therefore, the quiescent stage was somewhere between Days 5-7.

Both protocols will be useful in staging of cells for early or late week quiescent cell survival curve experiments on the Pantak 250 x-rays, simulating I-125 and Pd-103 energy's.

Radiological Parameters for CCL-16 cells

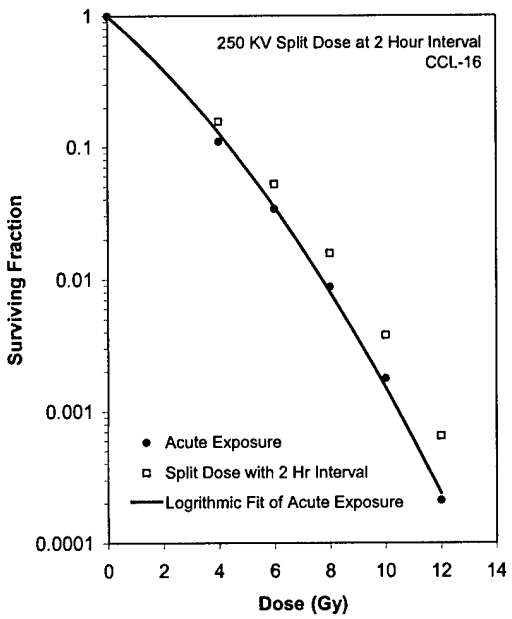

Figure 5

In order to measure the radiological parameters of the cells used in these studies, the acute exposure survival curves were measured using 250 kV x-rays. Split dose experiments were conducted to measure the half time of sublethal damage repair. The solid line in Figure 5 represents the measured survival curve for CCL-16 cell line for the 250 kV x-rays. Solid symbols represent acute exposure while the open symbols represent the survival when the single exposure dose is split into two equal doses separated by 2 hour interval. The cells are kept at 22^0C during the waiting interval to prevent proliferation. The α and β parameters were estimated by fitting the acute exposure curve to a LQ equation. The α and β for the 250 kV acute exposure were found to be 0.42

Gy^{-1} and 0.023 Gy^{-2}.

With β determined from the acute exposure survival curve, the sub-lethal damage repair time constant can be determined from the ratio of the survival measured from the split dose irradiation to that of single irradiation. The logarithm of this ratio is a quadratic function of total dose (Figure 6). The repair half time, using the incomplete repair model, is found to be 1.1 hours.

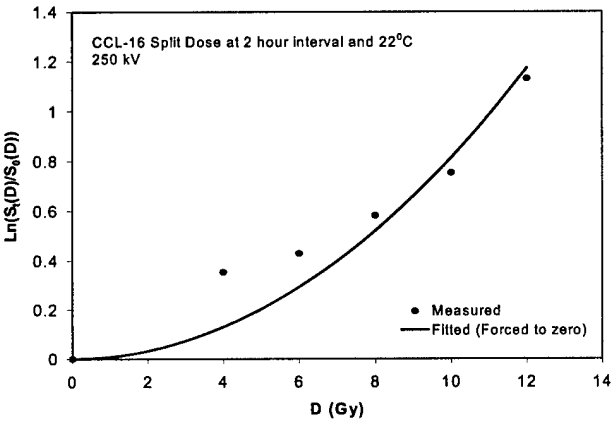

Figure 6

Radiological Parameters for BA1112 cells

Acute survival curves for BA1112 cell line for acute exposures using the simulated ^{125}I and ^{103}Pd x-ray beams were measured. Results are shown in Figure 7. The lines represent fit to LQ model using a fixed β. The parameters of α and β for the BA1112 cell line for ^{125}I and ^{103}Pd photons were determined from the survival curves obtained under acute exposure condition using simulated ^{125}I and ^{103}Pd x-ray beam on an orthovoltage unit. The acute survival curves for the simulated ^{125}I and ^{103}Pd x-rays were first fitted individually to LQ equation for α and β. The average of the β from these fits is then used as a fixed parameter in the fit of survival curves to determine the α for each simulated x-rays. The fitted α and β is given in table II.

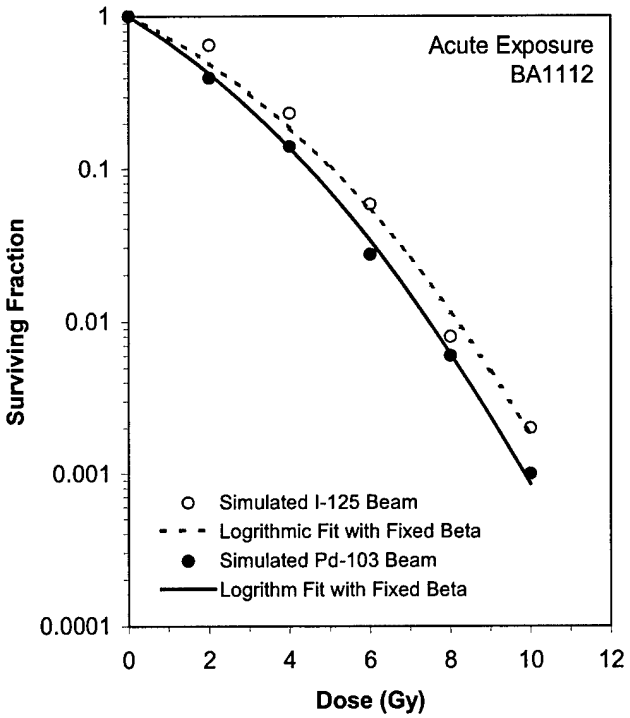

Figure 7

Split dose experiments were performed with 250 kV x-rays for BA1112 cell line. Results are shown in Figure 8. A total dose of 10 Gy was given. The survival fraction was measured as a function of time interval between two 5 Gy irradiation. The cells were kept at 22^0C during the waiting interval to prevent proliferation. According to incomplete repair model we have,

$$\frac{\ln[S(t)/S(0)]}{\ln[S(\infty)/S(0)]} = 1 - e^{-\mu t}$$

where S(t) is the surviving fraction with split time interval t and μ is the sub-lethal damage repair time constant. By fitting the measured data to the above equation, the repair half-time was found to be 19 minutes. The following table II summarizes the parameters determined for the BA1112 cell lines.

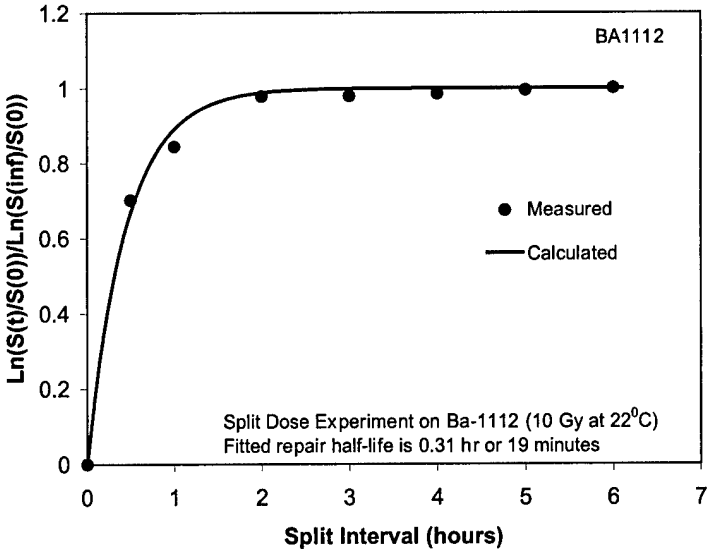

Figure 8

Tumor growth was measured for the BA1112 cell implanted in rat (Figure 9). The tumor growth curve is fitted to an exponential function of time. The tumor size doubling time is found to be 2.7 days.

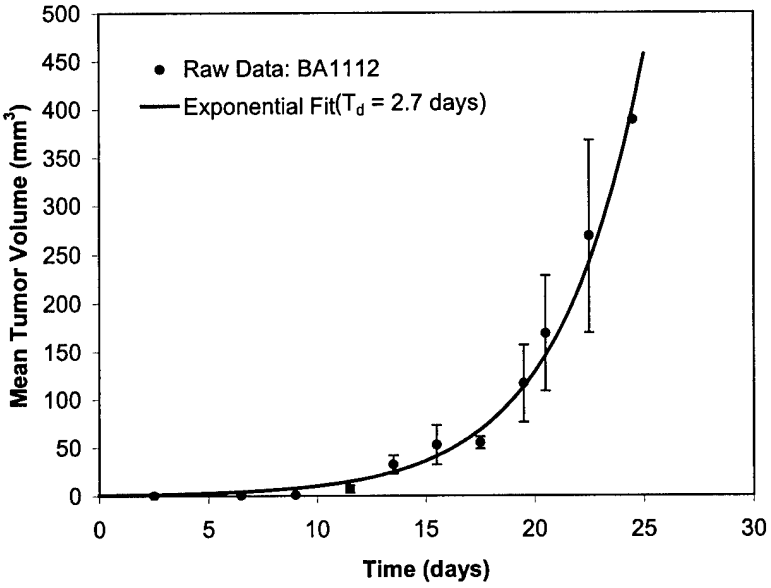

Figure 9

Table II. Radiological parameters for BA1112

Mean photon energy	Parameters for BA1112				
	α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)	Tumor Doubling Time (day)	Sub-lethal Damage Repair Half-time (hr)
^{103}Pd equivalent	0.35	0.035	10.1	2.7	0.314
^{125}I equivalent	0.28	0.035	7.9	2.7	0.314

In vivo tumor growth studies

In order to produce a consistent dose distribution to irradiate the tumors transplanted to different animals and to minimize radiation exposure to personnel handling the radioactive seeds, an afterloading seed applicator was designed and fabricated. The applicator was made of polystyrene with loading ports for nine seeds. The central portion of the applicator was open and has a dimension large enough for tumor to grow. Equal source strength was assigned to all nine seeds in order to minimize the possible confusion of handling variable source strengths. The seeding configuration was optimized to produce an, as uniform as possible, dose distribution to the central portion of the applicator and to be usable for both ^{125}I and ^{103}Pd seeds.

Twelve applicators were built to conduct a tumor cure experiment. A light-weight metallic helmet measuring 2.2 cm (cranial-caudal length) x 2.15 cm (side-side width) x 2.2 cm (height) was sutured to the rat's head by four stitches through the cartilage of the ears and two more stitches just behind the head at the neck. A seventh suture placed under the tumor will be tied to the central bar that across the top of the helmet, thus ensuring the tumor is pulled up into the center of the treatment volume. Treatment volumes were 2.3 cm^3 for ^{125}I or ^{103}Pd. The lightweight metallic helmet was afterloaded with the seed applicator. Calculated dose rates from each applicator are shown in tables III and IV.

Table III. Relative Initial Dose Rate for ^{125}I Draximage LS-1 Seeds

Dose Points	Relative Dose (%)						
	Center	3 mm (X)	4 mm (X)	5 mm (X)	3 mm (D)	4 mm (D)	5 mm (D)
9 mm up	126.7						
8 mm up	115.1	105.4	116.9	109.0	112.7	113.6	119.1
7 mm up	105.6	109.4	119.4	117.2	112.3	117.4	125.2
6 mm up	106.0	113.4	121.0	122.6	112.7	121.5	133.9
5 mm up	104.6	114.7	122.9	133.0	115.8	127.5	142.6
4 mm up	103.1	115.5	131.6	143.2	120.3	130.6	145.5
3 mm up	104.4	119.2	135.6	148.9	122.3	132.9	143.8
2 mm up	103.4	120.7	135.5	149.7	121.2	133.5	140.5
1 mm up	100.0	119.0	134.0	147.0	117.2	130.0	137.3
Base	94.8	111.8	125.9	137.6	111.2	121.2	127.6
1 mm down	87.2	99.7	112.0	121.1	101.7	110.7	114.6
2 mm down	78.1	84.8	94.4	100.6	89.3	96.6	100.1

Table IV. Relative Initial Dose Rate for ^{103}Pd Theragenic M200 Seeds

Dose Points	Relative Dose (%)						
	Center	3 mm (X)	4 mm (X)	5 mm (X)	3 mm (D)	4 mm (D)	5 mm (D)
9 mm up	120.2						
8 mm up	114.9	110.0	105.9	101.2	115.3	115.1	113.6
7 mm up	112.0	110.1	109.8	107.5	114.2	118.1	120.3
6 mm up	107.3	112.9	116.1	116.2	115.9	122.0	126.4
5 mm up	105.3	116.7	123.7	125.8	118.1	126.4	131.7
4 mm up	106.5	120.4	129.0	132.3	119.8	129.9	134.6
3 mm up	107.1	122.8	130.1	135.6	122.6	131.6	135.8
2 mm up	104.4	122.3	130.3	136.5	122.4	128.9	131.8
1 mm up	100.0	119.2	126.1	132.7	119.1	124.4	123.2
Base	94.9	112.2	118.9	124.2	111.4	115.9	113.5
1 mm down	88.1	100.9	107.3	111.1	99.7	103.8	101.5
2 mm down	78.9	88.3	93.1	95.1	84.7	88.0	86.7

The actual dose delivered for a given batch of seeds were verified by TLD point dose measurements for each applicator after it is removed from a rat at the completion of experiment. A jig, which models the fully-grown tumor on the head of a rat, is made of polystyrene. Two $1\times1\times1$ mm^3 micro-TLD cubes can be placed in the jig so that the TLD cube is at the center and 3 mm above the base of the applicator. The applicator and the associated helmet were placed on the jig to simulate the actual dose delivery. Three separate measurements were made for each applicator to minimize the effect of statistical uncertainties from TLD cubes. The irradiation duration is controlled so that the dose delivered to TLD is around 100 cGy for each irradiation. The use of the TLD dosimetry system follows strictly a well-established protocol in our laboratory. For each batch of TLD, the sensitivity of each cube, or chip factor, was determined by irradiating the TLDs to a known dose and comparing the TLD readings. To relate the TLD reading to dose

delivered by ^{125}I or ^{103}Pd seeds, a dose calibration was performed for a 6 MV photon beams on a Clinac-2100C linear accelerator. An energy correction factor, which takes into account of the energy response of the TLD, was then applied to yield the dose given by ^{125}I or ^{103}Pd. For the TLD verification measurements performed for the ^{125}I seeds, the correction factor of 1.41 from Meigooni and Nath was used. Table V compares the dose measured in polystyrene to the dose calculated to water at the same measurement point for six applicators. The measured dose in polystyrene is on the order of 5% higher than the calculated dose. Relative dose distribution in selected planes is being measured by using the GafChromic films.

Table V. Comparison of Dose Measured by TLDs for Six Applicators

Applicator	Measured (cGy)	Calculated (cGy)	Relative Difference (%)	Standard Deviation
I	124.3	114.2	1.089	0.02
L	102.1	96.7	1.056	0.00
F	87.9	83.6	1.051	0.04
G	79.7	74.8	1.067	0.02
B	87.1	82.5	1.050	0.09
H	82.0	78.3	1.047	0.04

Experiments were conducted using ^{125}I seeds with an initial dose rate of 8 cGy/hr. The response of the tumors to treatment was analyzed by measuring the tumors twice weekly until each tumor has reached a maximum volume of 1 cm^3 or until the tumor has regressed and the animal has been free of tumor for 100 days. Some of the results are shown in Figure 10. Tumor size growth curve includes both the growth in cell population and the increase in tumor growth supporting matrix such as blood vessels. Therefore a direct comparison between calculation must include the both factors in the model calculation. In the above figure, the calculation includes only the cell-kill and cell re-population. The cell doubling time in the tumor system, as opposed to the tumor size doubling time, was estimated from the total tumor cells counted in the tumor that has grown 21 days after an initial injection of 7500 cells to the rat. The cell doubling

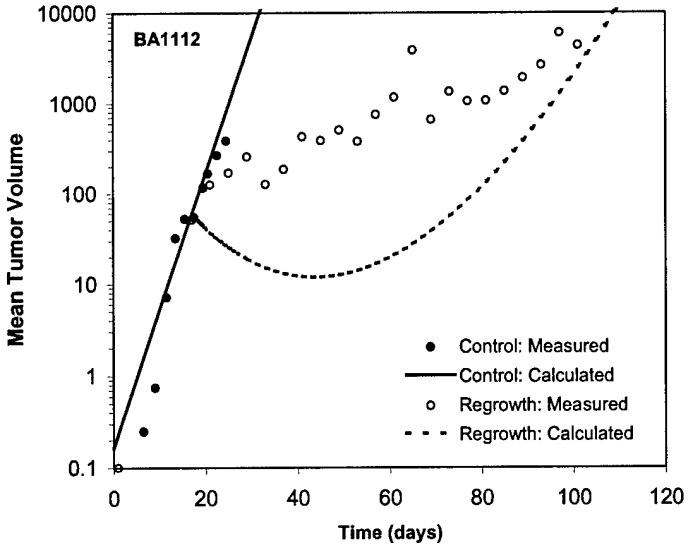

Figure 10.

time is estimated to be 2.1 days (as opposed to 2.7 days tumor size doubling time, as shown in Figure 9). The α, β, and repair half-time were determined directly from the measurements performed on the BA1112 cells. The calculated curve, with the radiation applied at day 17 of tumor growth, show an initial reduction of the total tumor cells. As time progress further, the cell re-population overcomes the radiation induced cell kill due to the low dose rate and grow at an apparent slower growth rate. Modeling the effect of tumor matrix grow is being pursued.

In vivo studies using an in vitro assay

In this experiment, BA1112 tumor cells were irradiated in vivo to graded doses from 2 to 20 Gy. Following irradiation at low dose rate, the tumours were removed and their colony formation ability was measured using our in vitro assay techniques. Figure 11 shows a comparison of the surviving fraction as a function of dose calculated for the BA1112 cells to that measured in an in vivo/in vitro experiment using CLDRI ^{125}I irradiation. The solid line represent the calculated survival curve using the average initial dose rates used in the experiments. The open circle represent calculation using the actual initial dose rate for each experiment. The parameters of α, β, repair half-time, and tumor doubling time were determined directly from the measurements performed on the BA1112 cells (details are provided separately).

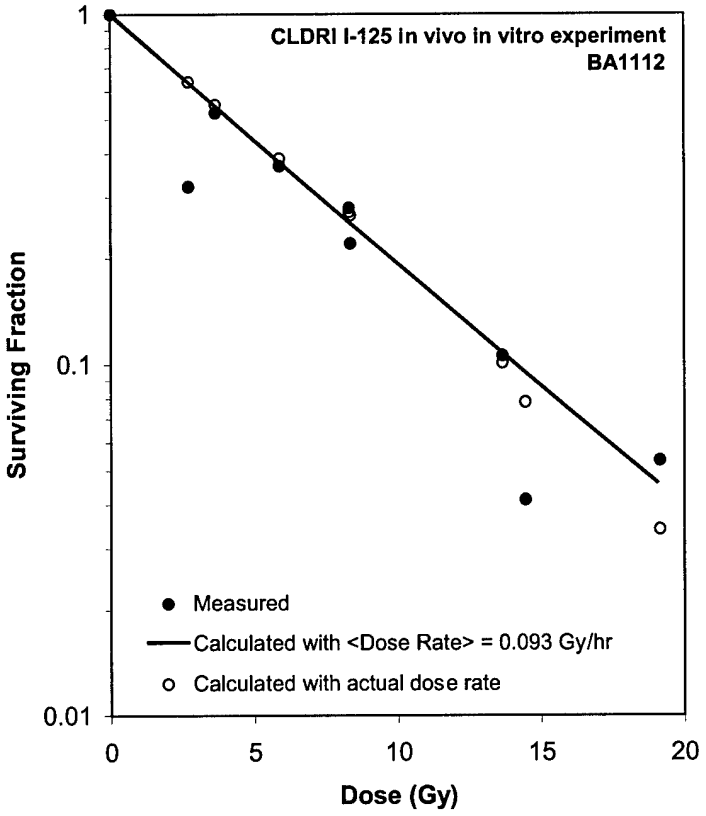

Figure 11

KEY RESEARCH ACCOMPLISHMENTS

- A theoretical model based on incomplete repair during CLDRI has been developed for addressing the questions raised in the project. The BED for implants with a mixture of two radionuclides has been derived as an analytical expression. A manuscript describing this work has been submitted for publication in International Journal of Radiation Oncology (see Appendix for details).

- Cell survival curves for both ^{125}I and ^{103}Pd were measured using monolayers of Chinese hamster cells in a petri dish irradiated at low dose rates using ^{125}I and ^{103}Pd sources. The dose sparing effect of 7 cGy/hr relative to 12 cGy/hr can be expressed by dose modifying factors of 2 ±0.6 and 1.5 ±0.5 for ^{103}Pd and ^{125}I, respectively. The RBEs of ^{103}Pd relative to ^{125}I were 1.2 ± 0.4 and 2.0 ± 0.5 for 7 and 12 cGy/hr, respectively. In our system, the RBE of ^{103}Pd at 19.7 cGy/hr relative to ^{125}I at 7.72 cGy/hr is estimated to be 3±1. A manuscript describing this work is in preparation.

- Cell survival curves for ^{103}Pd were measured using monolayers of BA1112 cells in a petri dish irradiated at low dose rates using ^{103}Pd sources. An orthovoltage x-ray machine was adapted to produce nearly monoenergetic 21 keV photons which simulates ^{103}Pd photon energies. Using this x-ray beam, cell survival curves for the BA1112 cells in a petri dish irradiated at an acute dose rate were also measured. We are now attempting to test our theoretical model for predicting the CLDRI survival curves in vitro for ^{103}Pd sources from the acute dose rate exposure data.

- Cell survival curves for ^{125}I were measured using of BA1112 cells irradiated in vivo at low dose rate of 8 cGy/hr using the afterloading rat applicator with ^{125}I sources. An orthovoltage x-ray machine was adapted to produce nearly monoenergetic 28 keV photons which simulates ^{125}I photon energies. Using this x-ray beam, cell survival curves for the BA1112 cells in a petri dish irradiated at an acute dose rate were also measured. We are now attempting to test our theoretical model for predicting the CLDRI survival curves in vivo for ^{125}I sources from the acute dose rate exposure data.

- In order to produce a consistent dose distribution to irradiate the tumors transplanted to different animals and to minimize the radiation exposure to personnel handling the radioactive seeds, an afterloading seed applicator has been designed. Twelve applicators were fabricated. Dose distributions produced by these applicators were calculated and verified by a series of dosimetry measurements. Several animals have been treated with CLDRI using these applicators containing ^{125}I seeds at 9 cGy/hr. Tumor growth was significantly slowed by CLDRI, from a tumor doubling time of 2.7 days in controls to 13 days in the treated animals. Further experiments and analysis are ongoing.

REPORTABLE OUTCOMES

A manuscript entitled "Biologically effective dose (BED) for interstitial seed implants containing a mixture of radio-nuclides with different half lives" by Zhe Chen,

Ph.D. and Ravinder Nath, Ph.D. has been submitted for publication in the International Journal of Radiation Oncology. The manuscript is attached as an Appendix.

CONCLUSIONS

We have made considerable progress towards the specific aims of the project. Theoretical model for continuous low dose rate irradiation using a mixture of radionuclides has been developed. Experiments have been performed using BA1112 tumor cells and Chinese Hamster cells growing in vitro and BA1112 cells growing in vivo as solid tumors in WAG/rij rats. Radiobiology parameters for these cells have been determined and used in the theoretical radiobiology model to improve our understanding of the experimental observations. We have designed and fabricated applicators for in vivo irradiations as well as developed the animal care procedures. We have performed in vivo experiments for tumor growth studies using the BA1112 rat model with ^{125}I seed applicators. Further experiments with ^{103}Pd and mixed radionuclides are in progress. The in vivo studies with the rat model have been very difficult to perform because of the nature of these brachytherapy experiments, which involve long irradiation times. We would focus on completing the studies using the rat model in the next year. We expect to prepare at least two manuscripts by the end of next grant year.

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Biologically effective dose (BED) for interstitial seed implants containing a mixture of radio-nuclides with different half lives

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Abstract

Purpose: To develop a tool for evaluating interstitial seed implants that contain a mixture of radionuclides with different half-lives and to examine the clinical implications of prescribing to an isodose surface for such an implant.

Methods and Materials: A linear-quadratic model for continuous low dose rate irradiation was developed for permanent implants containing a mixture of radionuclides. Using a generalized equation for the biological effective dose (BED), the effects of cell proliferation and sub-lethal damage repair were examined systematically for implants containing a mixture of radionuclides. The results were contrasted with those for implants using a single type of radionuclide. A head & neck permanent seed implant that contained a mixture of ^{125}I and ^{103}Pd seeds was used to examine the clinical implications of the isodose prescription for such implants.

Results: An equation of BED for implants containing any number of radionuclide types was obtained. For implants containing a mixture of radionuclides with different half-lives such as ^{125}I and ^{103}Pd, the dose as well as its temporal delivery pattern to a point is dependent on the relative dose contributions from different types of radionuclide. It can vary from point to point throughout the implant volume. Therefore the quantitative effects of cell proliferation and sub-lethal damage repair are spatially dependent in such an implant. For implants containing a mixture of ^{125}I and ^{103}Pd seeds, the prescription to an isodose surface becomes non-unique. If the prescription dose was based on existing clinical experience of using ^{125}I seeds alone, mixing ^{103}Pd seeds with ^{125}I seeds would decrease the cell survival in such implant. On the other hand, if the prescription dose was based on existing clinical experience of using ^{103}Pd seeds alone, mixing ^{125}I seeds with ^{103}Pd seeds in a same implant would create radiobiologically "cold" spots (i.e. an increase in cell survival from the clinical expectation) at locations where a major portion of prescription dose is contributed by the ^{125}I seeds. For fast-growing tumors, these "cold" spots can become significant.

Conclusions: When cell proliferation and sub-lethal damage repair are present during dose delivery, total dose alone is no longer sufficient for a complete characterization of an interstitial seed implant. In order to avoid radiobiological "cold" spots when radionuclides of different half-lives are mixed in a permanent implant, the dose prescription should be based on the clinical experience of using the longer half-life radionuclide. Biologically effective dose provides a tool to start examining the radiobiological effects of mixing different type of radionuclides in the same implant.

Key words: interstitial implant, biologically effective dose, iodine-125, palladium-103, brachytherapy, radiobiology

I. Introduction

Permanent implantation of encapsulated radioactive seeds in tumors has been used widely as a primary or adjuvant therapy for treating prostate and head & neck cancers [2,15,26-27,28,29]. At present, seeds that contain the radionuclide of ^{125}I or ^{103}Pd are routinely used for permanent interstitial implant [23]. The choice of radionuclide for a given implant has been influenced largely by the historical development of radioactive seeds and by the clinical experience accumulated with the use of each radionuclide [2,28]. One rarely mixes seeds of different radionuclide type in the same implant, due to the lack of existing clinical experience as well as the lack of appropriate tools for evaluating such an implant. Recently, two permanent seed implants, each containing a mixture of ^{125}I and ^{103}Pd seeds, have been carried out in our clinic for patients with head & neck cancers. The decision of using a mixture of ^{125}I and ^{103}Pd seeds in the same implant was based primarily on the clinician's intuition. The goal of this paper is to develop a proper tool for evaluating this type of implants.

The need for such a tool stems from the well-known observations in radiobiology that the cell survival in an interstitial implant depends not only on the total dose delivered but also on the temporal pattern of dose delivery [23]. For example, ^{125}I seeds emit photons with an average energy of 28 keV and its source strength decays exponentially as a function of time (with a half-life of 60 days). ^{103}Pd seeds, on the other hand, emit photons with lower average energy, about 21 keV, and its source strength decays with a much shorter half-life of 17 days. The variation in radioactive decay half-life gives rise to distinct temporal patterns in the delivery of a prescribed dose using different radionuclides. Figure 1 illustrates the dose delivered as a function of implant time for ^{125}I and ^{130}Pd implants. The time required to delivery, for example, 80% of total dose (dose to full decay) differs by a factor of more than three (about 140 days for ^{125}I implants and about 40 days for ^{130}Pd implants). Such a drastic difference in the temproal pattern of dose delivery could result in very different clinical responses at a given total dose if the surviving cells in the irradiated volume continue to proliferate and the sub-lethally damaged cells can be repaired during the dose delivery [7-9]. To take this dose delivery difference into account, the dose to full decay is commonly prescribed at a value of 145 Gy for ^{125}I implants which is considerably higher than the 125 Gy for ^{103}Pd implants for mono-therapy of prostate cancer. When seeds of different half lives are mixed in the same implant, the delivered dose as well as its temporal pattern to a given point within the implant are now depended not only on the spatial locations of the seeds but also on the type of radionuclide each seed contains. The temporal pattern of dose delivery becomes spatially dependent in such an implant. A treatment planning tool that can capture the interaction of the temporal pattern of dose delivery in a volume implant and the underlying tissue radiobiology is therefore needed in order to properly evaluate such an implant.

Radiation induced cell-inactivation, and the concept of biologically effective dose (BED), has often been used as a surrogate of the biological responses to ionizing radiation [1,5-8]. For acute irradiation, the linear-quadratic (LQ) model has been used to link the cell inactivation with the total delivered dose. The LQ model describes the radiobiological properties of the irradiated tissue by two model parameters (α and β)[7]. It has been widely used to examine the dependence of the overall cell-inactivation on the dose fractionation patterns in external beam radiotherapy. In protracted irradiation, the time dependent biological processes, e.g. the continuous

proliferation of the surviving cells and the time-dependent repair of sub-lethally damaged cells, may influence the effectiveness of different dose delivery patterns. Thames has extended the LQ model to continuous irradiation at a constant dose rate by taking into account the kinetics of sub-lethal damage repair during the dose delivery [27]. Later, Dale extended these concepts further to continuous irradiation with exponentially decreasing dose rate, manifested typically in the low dose-rate brachytherapy using a single type of radionuclide [5-6]. Dale's formulation, fundamentally equivalent to the incomplete repair model [27], takes into account both the cell proliferation and sub-lethal damage repair during a dose delivery characterized by exponentially decaying dose rates. These model introduced the concept of biologically effective dose (BED) as the dose which would produce the cell survival characterized by the equation $S = e^{-\alpha \cdot BED}$ for course of fractionated radiotherapy or brachytherapy [3,7]. The resulting formula for BED, despite the simplistic nature of the models for the cell proliferation and sub-lethal damage repair, offers a theoretical tool for systematic examination of the interplay between the temporal pattern of dose delivery and the underlying tissue properties. Ling has used the model to assess the relative radiobiological effectiveness of implants using radionuclide of different half lives[20] and to examine the biological effects of dose heterogeneity inherent to interstitial implant [19]. In this article, we show that Dale's equation for BED can be easily generalized for implants containing a mixture of radionuclides with different half lives. The potential of using the generalized BED formula as a tool for evaluating implants containing a mixture of radionuclides is examined. The usefulness of the generalized BED formula is illustrated by examining the clinical implications of isodose prescription for a head & neck implant containing a mixture of ^{125}I and ^{103}Pd seeds.

II. Methods and Materials

1. Dose Rate Calculation

To simplify discussion, an implant containing a mixture of radionuclides is defined as follows. Assume the implant consists of N seeds made of M different type of radionuclides, i.e.

$$N = \sum_{i=1}^{M} N_i$$

where N_i denotes the number of seeds containing radionuclide type i. The instantaneous dose rate to a point $\vec{r}$ at time t after the seed implantation is given by [22]

$$\dot{D}(\vec{r},t) = \sum_{i=1}^{M} \dot{D}_{0i}(\vec{r}) e^{-\lambda_i t} \qquad (1a)$$

where $\dot{D}_{0i}(\vec{r})$ is the initial dose rate due to seeds containing radionuclide i and for point-like source is approximately equal to

$$\dot{D}_{0i}(\vec{r}) \approx \sum_{l=1}^{N_i} \frac{S_{il}\Lambda_i r_0^2}{|\vec{r}_{il} - \vec{r}|^2} g_i(|\vec{r}_{il} - \vec{r}|)(\bar{\phi}_{an})_i \qquad (1b)$$

In Eq.(1), the index i labels the radionuclide type and the index l labels the individual seeds. S_{il} denotes the air-kerma strength for the seed l of radionuclide type i. Λ_i, λ_i, $(\bar{\phi}_{an})_i$, and $g_i(r)$ denote the dose-rate constant, the radioactive decay constant, the anisotropy constant, and the radial dose function, respectively, for the seeds of radionuclide type i. r_0 denotes the reference distance (usually 1 cm) at which the dose-rate constant was determined. In this study, the delivered dose,

isodose distribution, and dose-volume histograms used in conventional implant dose evaluation were computed by using Eq. (1) with appropriate parameters for ^{125}I and ^{103}Pd seeds [22].

2. Linear Quadratic Model for CLDRI

The kinetics of cell proliferation and sub-lethal damage repair for continuous low dose rate irradiation (CLDRI) were modeled as follows [5-6]. The cell proliferation was characterized by a tumor potential doubling time T_p so that the total number of tumor cells at any time t, N(t), is related to the number of cells present at a reference time t_0, N(t_0), by

$$\begin{aligned} N(t) &= N(t_0)\cdot 2^{(t-t_0)/T_p} \\ &= N(t_0)\cdot e^{\ln 2\cdot(t-t_0)/T_p} \end{aligned} \tag{2}$$

The fast-growing tumors have shorter T_p and the slow-growing tumors have longer T_p. The tumor potential doubling time is tumor-type dependent and may vary from patient to patient even among the same tumor type. For squamous cell head & neck cancer, a "typical" T_p of 5 days have been quoted in literature [24]. For prostate carcinoma, T_p ranging from 10 to 60 days have been reported in the literature [10]. It should be pointed out that the use of Eq. (2) assumes that the cells in a target volume all proliferate at the same rate and cell loss from the tumor volume is negligible.

To model the repair of sub-lethal damage, Dale has invoked the assumption that radiation-induced cell inactivation is caused by the damage of two critical targets in a cell [5-6]. When a radiation event damages only one critical target, the cell is considered sub-lethally damaged, which is repairable. Cell inactivation occurs only when the other critical target is damaged before the existing damage is fully repaired. Dale assumed that sub-lethal damage repairs exponentially with time, i.e. if a sub-lethal damage was inflicted at time t_0, then the probability for it persisting to time t is $e^{-\mu(t-t_0)}$. Here the constant μ models the rate of repair and is related to the sub-lethal damage repair half-time, $T_{1/2}^{(R)}$, by

$$T_{1/2}^{(R)} = \frac{\ln 2}{\mu} \tag{3}$$

Average repair half-times reported for mammalian tissues vary from 0.5 to 3 hours [3].

3. Biologically effective dose for CLDRI with a mixture of radionuclides

The biologically effective dose has been defined as a dose-equivalent that would produce the expected cell survival characterized by an equation $S = e^{-\alpha\cdot BED}$ for a course of fractionated radiotherapy or brachytherapy [3,7]. Here α describes the tumor cell radiosensitivity as given by the LQ model [7]. Using the models of sub-lethal damage repair and cell proliferation described above, Dale derived an expression of BED for implants containing a single type of radionuclide, i.e,

$$BED = D(T_{eff})RE - \frac{0.693T_{eff}}{\alpha T_{pot}}. \tag{4}$$

The first term on the right-hand-side of the Eq.(4) is a product of the total dose delivered up to time T_{eff} and a factor RE that characterizes the relative effectiveness of the radiation. The second term on the right-hand-side describes the decrease in dose equivalent due to cell proliferation during CLDRI. In Eq.(4), T_{eff} denotes an effective treatment time at which the rate of tumor cell proliferation begins to exceed the rate of cell inactivation caused by the instantaneous dose deposited at T_{eff} (a situation unique to brachytherapy due to the exponentially decreasing dose rate given by a radionuclide. We will discuss the determination of T_{eff} further in the next section). Thus, dose delivered after the time T_{eff} produces no net tumor cell reduction. The relative effectiveness RE is given by

$$RE = 1 + 2(\frac{\beta}{\alpha})\frac{\gamma}{D(T_{eff})} \tag{5a}$$

with

$$\gamma = \frac{\dot{D}_0^2}{\mu - \lambda}\left\{\frac{1}{2\lambda}(1 - e^{-2\lambda T_{eff}}) - \frac{1}{\lambda + \mu}(1 - e^{-(\mu+\lambda)T_{eff}})\right\} \tag{5b}$$

where $\dot{D}_0$ denote the initial dose rate and $D(T_{eff}) = \frac{\dot{D}_0}{\lambda}(1 - e^{-\lambda T_{eff}})$. According to Eqs. (4) and (5), the relative effectiveness of a given radiation is dependent on the repair of sub-lethal damages. When sub-lethal damage is non-repairable (i.e. $\mu = 0$), $\gamma = D^2(T_{eff})/2$ and $RE = 1 + (\beta/\alpha)\times D(T_{eff})$, which is the same as the equation in the case of acute irradiation of a dose of $D(T_{eff})$. If, on the other hand, the sub-lethal damage can be repaired instantly (i.e. $\mu = \infty$), then $\gamma = 0$ and RE equals to unit. In this case, cell inactivation results from the simultaneous damage of two critical targets in the cell by a single radiation event. In general, the RE depends on the ability of sub-lethal damage repair and on the half-life of the radionuclide. The presence of cell proliferation, on the other hand, will always reduce the overall BED of a given radiation, as part of the dose has to be used to inactivate the repopulated cells. In this study, we generalize the Dale's expression to implants containing a mixture of radionuclide with different half-lives (see Appendix for details). For implants that contains a mixture of radiouclide with two different half-lives, the γ in Eq.(5) is given by

$$\begin{aligned}
\gamma = & \frac{\dot{D}_{01}^2}{\mu - \lambda_1}\left\{\frac{1}{2\lambda_1}(1 - e^{-2\lambda_1 T_{eff}}) - \frac{1}{\lambda_1 + \mu}(1 - e^{-(\mu+\lambda_1)T_{eff}})\right\} \\
& + \frac{\dot{D}_{02}^2}{\mu - \lambda_2}\left\{\frac{1}{2\lambda_2}(1 - e^{-2\lambda_2 T_{eff}}) - \frac{1}{\lambda_2 + \mu}(1 - e^{-(\mu+\lambda_2)T_{eff}})\right\} \\
& + \frac{\dot{D}_{01}\dot{D}_{02}}{\mu - \lambda_1}\left\{\frac{1}{\lambda_1 + \lambda_2}(1 - e^{-(\lambda_1+\lambda_2)T_{eff}}) - \frac{1}{\lambda_2 + \mu}(1 - e^{-(\mu+\lambda_2)T_{eff}})\right\} \\
& + \frac{\dot{D}_{01}\dot{D}_{02}}{\mu - \lambda_2}\left\{\frac{1}{\lambda_1 + \lambda_2}(1 - e^{-(\lambda_1+\lambda_2)T_{eff}}) - \frac{1}{\lambda_1 + \mu}(1 - e^{-(\mu+\lambda_1)T_{eff}})\right\}
\end{aligned} \tag{6}$$

where $\dot{D}_{01}$ and $\dot{D}_{02}$ denote the initial dose rates at the point of calculation produced by seeds containing radionuclide type 1 and 2, respectively; and $D(T_{eff}) = \frac{\dot{D}_{01}}{\lambda_1}(1-e^{-\lambda_1 T_{eff}}) + \frac{\dot{D}_{02}}{\lambda_2}(1-e^{-\lambda_2 T_{eff}})$. It is easy to shown, by examining Eqs.(5) and (6), that when radionuclide of different half-lives are mixed in the same implant the resulting BED does *not* equal to the simple addition of the BEDs from each radionuclide type alone.

III. Results

The use of BED for implants containing a single type of radionuclide has been discussed in several publications [3-6, 19-20]. In this section, we examine the properties of BED for permanent seed implants with a mixture of ^{125}I and ^{103}Pd seeds and compare them to implants using a single type of radionuclide. The use of BED is illustrated later by examining the isodose prescription for a clinical head & neck permanent seed implant containing a mixture of ^{125}I and ^{103}Pd seeds.

1) Effects of sub-lethal damage repair

To examine the effects of sub-lethal damage repair for permanent seed implants, let us consider first a special case: a permanent implant with no cell proliferation (i.e. $T_p = \infty$ in Eq.(6)). In absence of cell proliferation, the T_{eff} is determined by the time at which a treatment is physically terminated and is infinite for permanent implants. Setting T_{eff} to ∞ in Eq.(6) and Eq.(5), we have

$$RE = 1 + \frac{\beta}{\alpha} \frac{\dfrac{\dot{D}_{01}^2}{\lambda_1(\lambda_1+\mu)} + \dfrac{\dot{D}_{02}^2}{\lambda_2(\lambda_2+\mu)} + 2\dfrac{\dot{D}_{01}\dot{D}_{01}(\lambda_1+\lambda_2+2\mu)}{(\lambda_1+\lambda_2)(\lambda_1+\mu)(\lambda_2+\mu)}}{\dfrac{\dot{D}_{01}}{\lambda_1} + \dfrac{\dot{D}_{02}}{\lambda_2}} \qquad (7)$$

for implants with a mixture of radionuclides and

$$RE = 1 + \frac{\beta}{\alpha}\frac{\dot{D}_{01}}{\lambda+\mu} \qquad (8)$$

for implants with a single type of radionuclide. Since the BED is simply the product of the total dose and RE, it is suffice to examine the effect of sub-lethal damage repair on RE alone when the prescribed dose is fixed.

In the limiting cases where the sub-lethal damages are not repairable ($\mu = 0$) or can be repaired instantly ($\mu = \infty$) the total delivered dose alone would be sufficient to characterize both types of implants. For sub-lethal damage that repairs with a finite period of time, the relative effectiveness of the radiation would fall in between the values of the two limiting cases. The RE as a function of repair half-time is plotted in Fig.2 for a total dose of 80 Gy (80 Gy was chosen as it was the prescription dose for the head & neck case to be discussed later). The curves in the upper panel represent implants using a single type of radionuclide (^{125}I or ^{103}Pd) and the curves in the lower panel are for implants using a mixture of ^{125}I or ^{103}Pd seeds. The general trend exhibited in Fig.2, i.e. RE increases with increasing repair half-time, is intuitively correct as the total cell-inactivation is expected to increase when sub-lethal damage repair becomes less

efficient (i.e. longer repair half-times). The overall trend of RE between $T_{1/2}^{(R)} = 0$ and $T_{1/2}^{(R)} = \infty$ is depicted in the insert of the upper panel.

Figure 2 indicates that the dose delivered by using ^{103}Pd seeds alone would yield more cell-inactivation as compared to the same dose delivered by using ^{125}I seeds alone when there is repair of sub-lethal damage. This advantage of using ^{103}Pd seeds alone would increase initially as repair half-time becomes larger and would diminish eventually when sub-lethal damage becomes irreparable. Since the radiobiological effectiveness (RBE) arising from different LET [16], secondary electrons generated by ^{125}I and ^{103}Pd photons, is not dealt with in this paper, the differences illustrated here are resulted purely from the different decay half-lives of the two radionuclides. Because the decay half-life is shorter for ^{103}Pd seeds as compared to the ^{125}I seeds, the initial dose rate would be much greater for implants using ^{103}Pd seeds to deliver the same prescribed dose. The trend illustrated in Fig.2 is consistent with the dose-rate effect observed over the years for protracted dose delivery, albeit the dose-rate is now time dependent in the permanent implants.

When a mixture of ^{125}I and ^{103}Pd seeds is used in the same implant, the RE depends on both the repair half-life and the relative dose contribution from the two types of radionuclide as shown in the lower panel of Fig. 2. By varying the relative dose contribution from ^{125}I and ^{103}Pd seeds, the RE for the mixed-seed implant can be varied continuously from that of using ^{125}I alone to that of using ^{103}Pd alone. In such an implant, the BED calculated by Eq.(7) is able to provide a quantitative characterization of the effect of spatially dependent differential dose contribution from the ^{125}I and ^{130}Pd seeds. While Fig.2 was plotted for the total dose of 80 Gy, the qualitative trend shown here remained the same for other delivered doses. The magnitude of both RE and BED, however, would increase with the increase of total dose for both types of implant.

2) Effects of cell proliferation

Equations (4) and (6) also capture the effect of cell proliferation in a protracted permanent seed implant. To simplify the discussion, we assume, for the moment, that there is no sub-lethal damage repair. Setting μ to zero in Eq.(6) yields a BED as a function of implant time t,

$$BED(t) = TD(t) \times \left[1 + \frac{\beta}{\alpha} \cdot TD(t)\right] - 0.693t/(\alpha T_p) \qquad (9)$$

for implants with or without a mixture of radionuclides. The general conclusion remains the same for the case in which the sub-lethal damage can be repaired instantly (in this case, Eq.(9) would reduce to $BED(t) = TD(t) - 0.693t/(\alpha T_p)$). In Eq.(9), the TD(t) denotes the total dose delivered up to the implant time t and the second term on the right-hand-side describes the effect of cell proliferation. The presence of cell proliferation would always reduce the magnitude of BED, since part of the delivered dose has to counter the repopulated cells [5, 20]. The amount of reduction, $0.693t/(\alpha T_p)$, depends on both the proliferation rate ($0.693/(\alpha T_p)$) and the implant duration (t). It is important to note that if the proliferation rate remains the same during the dose delivery, there would exist a time at which the cell inactivation rate induced by the decaying instantaneous dose rate would become less than the proliferation rate. Beyond this time, there would be no net cell-inactivation advantage from the remaining dose delivered. The effective treatment time, T_{eff}, is defined as the time at which the cell inactivation rate equals to the

proliferation rate. Equation (9) also implies that a minimum total dose is required for an implant in order to produce a net cell-inactivation (*i.e. for BED > 0*) if cell proliferation is present at the onset of the implant.

The BED calculated at T_{eff} depends on both the cell proliferation rate and the radionuclide's decay half-life. Figure 3 shows the BED as a function of the potential tumor doubling time for a total delivered dose of 80 Gy. Note that the magnitude of BED much lager than the total delivered dose due the assumption that the sub-lethal damage repair is not repairable. The qualitative properties of Fig. 3 remain the same for other sub-lethal damage repair capabilities. The BED for implants with ^{125}I or ^{103}Pd alone are shown in the upper panel and the BED for implants with a mixture of ^{125}I and ^{103}Pd seeds are shown in the lower panel. As shown in Fig.3, the BED increases with T_p for both types of implants. This is because large T_p represent slow-growing tumors which give rises to small cell proliferation rate, hence needing less dose to combat the repopulated cells. For a given tumor proliferation rate, implants that deliver the same total dose within a shorter period of time will result in a larger BED. Therefore the BED for a ^{103}Pd implant will always be larger than that for an ^{125}I implant for the same delivered dose at any given tumor potential doubling time (see upper panel of Fig.3). When the two type of seeds are mixed in the same implant (lower panel of Fig.3), the general trend of BED as a function of T_p remained the same as that for implants with a single radionuclide type. The magnitude of BED at a given T_p, however, becomes dependent on the relative contributions of physical dose from the two types of radionuclide. The resulting BED can be turned from that of ^{125}I implant alone to that of ^{103}Pd implant alone by varying the relative dose contributions.

3) Permanent seed implant with a mixture of radionuclides: a clinical example

When both cell proliferation and sub-lethal damage repair are present, Eq.(4) and (6) can be used to calculate the BED for implants using a mixture of radionuclides. For the calculated BED to be clinically meaningful, one would have to know the patient specific tumor potential doubling time and the sub-lethal damage repair half-time. Given the simplistic nature of the biological model and the lack of reliable means of determining the patient specific model parameters at present, it would be inappropriate to treat the calculated BED as a quantitative predictor of the clinical outcome for a patient implant. However, the BED can be indicative of the relative merits between implants that utilize different physical implant strategies using a consistent set of radiobiological model parameters. It is on this premise, we regard the concept of BED a valuable tool for evaluating the quality of permanent seed implants. As shown in the previous sections, it allows a quantitative characterization of the interplay between the complicated temporal pattern of dose delivery exhibited in implants with a mixture of radionuclides and the underlying radiobiological processes. In the following, we illustrate the use of Eq.(4) and (6) on a head & neck implant using a mixture of ^{125}I and ^{103}Pd seeds by examining the implications of prescribing to a physical isodose line for such an implant.

The patient was a 45 years old male who presented with cancer of larynx. A permanent seed implant was performed to the post pharyngeal wall using ten ^{125}I seeds and twenty-three ^{103}Pd seeds. Based on the reconstructed seed locations from the seed localization films, dose to full decay was calculated using Eq.(1) and the isodose lines were created and projected to the corresponding radiographic films. Fig.4 shown the isodose lines (to full decay), in the XY plane

through the center of the implant, resulted from the ^{125}I seeds alone (top panel), from the ^{103}Pd seeds alone (middle panel), and from both type of seeds implanted (bottom panel). The 80 Gy isodose line was chosen by the physician for the implant. The initial source strength was 0.64 U for ^{125}I seeds and 0.88 U for ^{103}Pd seeds.

The basic issue regarding the dose prescription for such an implant is as follows. For a permanent implant using only a single type of radionuclide, the total dose, TD, at any given point is related to the initial dose rate, $\dot{D}_0$,

$$TD = 1.44 T_{1/2} \dot{D}_0 \qquad (10)$$

For this type of implant, a prescription to an isodose line is equivalent to a prescription to a corresponding isodose-rate line. In other word, the initial dose rate is fixed once a prescription to total dose is established. The temporal dose delivery pattern is the same throughout the implant.

When an implant contains a mixture of two radionuclides, equation (10) becomes

$$TD = 1.44 T_{1/2}^{(1)} \dot{D}_0^{(1)} + 1.44 T_{1/2}^{(2)} \dot{D}_0^{(2)} \qquad (11)$$

The total dose is now dependent on the initial dose-rates produced by the two types of radionuclide at the point of interest. According to Eq.(11), a prescription to an isodose line can now be fulfilled by many different combinations of $\dot{D}_0^{(1)}$ and $\dot{D}_0^{(2)}$. Therefore the prescription to an isodose line is now *not* unique with respect to the initial dose rates of the two types of radionuclide. Furthermore, the overall temporal pattern of dose delivery now varies throughout the implant. In absence of cell proliferation and sub-lethal damage repair, this non-uniqueness would have caused no detectable clinical consequences as the total dose alone would be sufficient for characterizing the implant (see earlier discussion). However, as was shown earlier, when cell proliferation and sub-lethal damage repair are present, the effective cell-inactivation becomes dependent on the relative dose contributions, i.e. $\dot{D}_0^{(1)}$ and $\dot{D}_0^{(2)}$, of the two types of radionuclide and their temporal patterns.

To examine the clinical implications of prescribing to the an isodose line for this head & neck implant, let us examine, for the moment, a single spatial point on the isodose line. The total dose to this point is 80 Gy and the contributions from the ^{125}I seeds and ^{103}Pd seeds to the point can be determined from the seed locations in the implant. Figure 5 plotted the calculated BED as a function of tumor potential doubling time for all possible dose contributions by ^{125}I and ^{103}Pd seeds. A repair half-life of 1.5 hr and a α/β of 10 were used in the calculation. It is seen from Fig.5 that the BED is largest if the entire prescribed-dose to the point is contributed by ^{103}Pd seeds (for any tumor potential doubling times). At a given T_p, the BED decreases as the proportion of prescribed dose contributed by the ^{125}I seeds increases, and attains a minimum value when the full prescription dose is given by ^{125}I seeds. The reduction in BED with the increased dose contribution by ^{125}I seeds is most significant for fast growing tumors and becomes less significant for slower growing tumors.

The BED calculated with the actual dose contributions from ^{125}I and ^{103}Pd seeds for head & neck implant at 19 different spatial locations on the 80Gy isodose line is plotted in Fig.6 for several potential doubling times. The following observations can be made from Figs. 5 and 6. First, for fast growing tumors, those locations on the prescribed isodose line with dose

contributed primarily by ^{103}Pd seeds will have considerably more effective cell kill than the locations with dose contributed primarily by the ^{125}I seeds, almost a order of magnitude reduction in BED; Secondly, the difference in the differential cell kill become less significant for slow growing tumors. Therefore if the dose prescription was established from existing implant experience that uses ^{125}I seeds only, mixing ^{103}Pd seeds with ^{125}I seeds would always increase the effective cell-inactivation for the same dose prescription. On the other hand, if the dose prescription was established from implant experience of using ^{103}Pd seeds alone, mixing ^{125}I seeds with ^{103}Pd seeds in the same implant would create radiobiologically "cold" (less cell-inactivation than expected from the existing clinical experience) spots at locations where more dose is contributed by the ^{125}I seeds. These "cold" spots can become significant for fast growing tumors. The dose prescription for the clinical case was based on experience of using ^{125}I seeds alone. Therefore mixing the ^{103}Pd seeds with ^{125}I seeds in this implant, at the least, did not reduce the treatment effectiveness from the priori clinical expectation.

For a complete evaluation of the effect of isodose prescription, BED at locations other than those on the prescription isodose line should also be calculated as the total dose and initial dose rates contributed by ^{125}I and ^{103}Pd seeds are spatially dependent. The basic conclusions drawn above would remain the same.

Discussions

Due to the protracted nature of dose delivery associated with the permanent seed implants, the presence of sub-lethal damage repair and cell proliferation in the irradiated volume requires new tools to characterize the interplay of the physical dose delivery characteristics and the underlying biological processes. As shown in this work, the BED formula derived by Dale [5-6] can be easily generalized for permanent implants containing a mixture of radionuclides. The general conclusions drawn from the model calculation, as shown in the previous section, are physically plausible and conform to the common intuition. However, it should be pointed out that the quantitative numbers of BED should be viewed in the context of the limitations inherent in the models. We hope the concept of BED and the generalized BED equation for implants with a mixture of radionuclides would help stimulating more research interests in exploring a realistic description of the interplay of physical dose delivery and the underlying radiobiological processes.

It should be emphasized that radiobiological modeling is intrinsically organ specific. For a given organ, factors important to the calculation of BED include the physical dose and its temporal dose delivery pattern, tumor intrinsic dose response characteristics (α and β), potential tumor doubling time, and sub-lethal damage repair rate. Although not considered in the current model, other factors that affects the radiobiological responses of tissues such as the presence of hypoxic cells [12], cell cycle effects [13], and radiation induced apoptosis [17-18] and organ architecture should be considered as well for a complete radiobiological characterization. At present, however, not all factors are well understood and/or quantitatively characterized. In addition, some of these factors are known to vary from patient to patient even in the same type of organ tissue. From this point of view, one should be cautioned in using these indices in quantitatively in dose prescription: they are not meant to and should not be used as an absolute index for the treatment outcome on a given patient. Nonetheless, BED provides the best available

description of the interplay of physical dose with the radiobiology. When a given set of radiobiological parameters are used consistently, they are very useful in estimating the treatment efficacy of different brachytherapy applications and in evaluating competing treatment plans.

Dose distribution from interstitial brachytherapy is inherently inhomogeneous. Since the BED is determined by the dose and its temporal delivery pattern at each spatial point, calculation of BED at each spatial point is needed for a complete evaluation of a planned implant. With the advance of medical imaging modalities and image-based treatment planning [21], we hope that three dimensional tissue structures can be identified more accurately and a 3-D distribution of BED can be calculated with confidence [14]. With the BED distribution, radiobiologically significant "cold" spots, due either to "cold" spots in total dose or to the "cold" spots in dose-rate, can be identified during the planning of an interstitial seed implant.

IV. Conclusions

A generalized Dale equation for biologically effective dose is presented for interstitial implants containing a mixture of radionuclides of different half-lives. It was shown, based on the BED model, that the effective cell survival from an interstitial seed implant is dependent not only on the total delivered dose but also on the temporal pattern of the dose delivery when cell proliferation and sub-lethal damage repair are present. For implants containing a mixture of radionuclides, the dose to a point as well as its temporal delivery pattern is determined by the relative dose contributions from different types of radionuclide that can vary throughout the implant volume. Therefore the quantitative effects of cell proliferation and sub-lethal damage repair are spatially dependent in such an implant. Biologically effective dose provides a tool to begin examining the radiobiological effects of mixing different type of radionuclides in a same implant. The model calculation suggests that adding ^{103}Pd to ^{125}I implant would increase the effectiveness of cell-inactivation while the opposite is not true if the dose prescription was based on the clinical experience established with the single radionuclide-type implants. It is hoped that this work would stimulate further research interest to improve the radiobiological modeling.

Appendix:

Eq.(4) can easily be derived following the work of Dale [5-6] for implants containing a single type of radionuclide. The reader is referred to Dale's original articles [5-6] for the detailed steps and the rationale underlying the derivation. The main derivation steps are outlined below.

Dale has invoked the assumption that a lethal radiation damage is caused by the damage of two critical targets in a cell. When the two critical targets are damaged simultaneously by a radiation event, the resulting lethal damage is termed type-A damage. When a radiation event damages only one critical target, the cell is considered sub-lethally damaged, which is repairable. In the later case, a lethal damage results when the second critical target is damaged before the existing sub-lethal damage is fully repaired. This type of lethal damage is termed type-B damage. The type-A damage is always proportional to the total delivered dose irrespective of dose rate while the type-B damage is dose-rate dependent since the independently damaged targets may be repaired over time. The overall radiation induced cell inactivation is therefore proportional to the sum of type-A and type-B damages. The main goal in deriving the biologically effective dose is to determine the total probability of type-A and type-B damages over the time period of a given dose delivery.

For an implant with a mixture of radionuclides, the instantaneous dose rate to a point of interest at time t after the implant is given by Eq.(3) in the main text as

$$\dot{D}(t) = \sum_{i=1}^{M} \dot{D}_{0i} e^{-\lambda_i t} \qquad \text{(A1)}$$

where the summation is over different types of radionuclides used in the implant. Using this expression for instantaneous dose rate, the derivation for BED follows almost exactly the same steps outlined in the Appendix of Dale's article [5-6].

The type-A damage is proportional to the dose delivered. Therefore, the total type-A damage accumulated over a period of time T after seed implantation is given by

$$\text{Total type - A damage} = \alpha \sum_i \frac{\dot{D}_{0i}}{\lambda_i}(1 - e^{-\lambda_i T}) \qquad \text{(A2)}$$

The type-B damage is determined by the joint probability of two targets being damaged at different times by two different radiation events. By assuming the sub-lethal damage repairs exponentially with time, the total type-B damage accumulated over the same period of time T after seed implantation can be determined.

$$\text{Total Type - B damage} = 2\beta \sum_i \sum_j \frac{\dot{D}_{0i}\dot{D}_{0j}}{\mu - \lambda_i}\left\{\frac{1}{\lambda_i + \lambda_i}(1 - e^{-(\lambda_i+\lambda_j)T}) - \frac{1}{\lambda_j + \mu}(1 - e^{-(\mu+\lambda_j)T})\right\} \qquad \text{(A3)}$$

In the above expressions, α and β are the linear and quadratic coefficients, respectively, of the linear-quadratic cell inactivation model. μ is the repair time constant that characterizes the rate of sub-lethal damage repair.

With Eqs.(A2) and (A3), the ratio of total lethal damage to the type-A lethal damage alone, termed as relative effectiveness by Dale, can be determined as

$$\mathrm{RE} = 1 + \frac{\text{Total type - B damage}}{\text{Total type - A damage}}$$

$$= 1 + 2\left(\frac{\beta}{\alpha}\right)\frac{\sum_i \sum_j \frac{\dot{D}_{0i}\dot{D}_{0j}}{\mu - \lambda_i}\left\{\frac{1}{\lambda_i + \lambda_i}(1 - e^{-(\lambda_i+\lambda_j)T}) - \frac{1}{\lambda_j + \mu}(1 - e^{-(\mu+\lambda_j)T})\right\}}{\sum_i \frac{\dot{D}_{0i}}{\lambda_i}(1 - e^{-\lambda_i T})} \qquad \text{(A4)}$$

Equation (A4) is the main result of this derivation. The biologically effective dose (BED) for an implant with a mixture of radionuclides is therefore given by

$$\mathrm{BED} = \sum_i \frac{\dot{D}_{0i}}{\lambda_i}(1 - e^{-\lambda_i T_{eff}})RE - KT_{eff} \qquad \text{(A5)}$$

where $K = \ln 2/(\alpha T_p)$ and T_p is the tumor potential doubling time. Note that T_{eff} is the effective treatment time at which the tumor cell-proliferation rate exceeds the tumor cell-inactivation rate caused by the instantaneous dose rate at that time.

As expected, for implants with a single type of radionuclide, i = j = 1, Eq. (A4) and Eq.(A5) reduces to Dale's original equation

$$\mathrm{RE} = 1 + 2\left(\frac{\beta}{\alpha}\right)\dot{D}_0 \frac{\lambda}{\mu - \lambda}\frac{1}{(1 - e^{-\lambda T})}\left\{\frac{1}{2\lambda}(1 - e^{-2\lambda T}) - \frac{1}{\lambda + \mu}(1 - e^{-(\mu+\lambda)T})\right\} \qquad \text{(A6)}$$

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Figure Captions:

Figure 1 Accumulative dose delivered as a function of implant time for ^{125}I and ^{103}Pd implants. Note that the vertical axis was plotted as the ratio of delivered dose to the dose to full decay for the two radionuclides.

Figure 2 Relative effectiveness calculated as a function of repair half-time for implants using a single type of radionuclide (upper panel) and for implants using a mixture of ^{125}I and ^{103}Pd seeds (lower panel). The insert in the upper panel illustrates the behavior of RE over a large range of repair half-time.

Figure 3 Biologically effective dose calculated as a function of potential doubling time for implants using a single type of radionuclide (upper panel) and for implants using a mixture of ^{125}I and ^{103}Pd seeds (lower panel). Sublethal damages are assumed not repairable in this plot. See text for a discussion on the magnitude of the BED in this case.

Figure 4 Dose distribution on the XY plane for the head & neck implant using ^{125}I seeds alone (top), ^{103}Pd seeds alone (middle), and from the mixed-seed implant (bottom). The 80 Gy isodose line on the bottom panel was chosen as the clinical prescription isodose.

Figure 5 Biologically effective dose for an 80 Gy implant using a mixture of ^{125}I and ^{103} Pd seeds, as a function of tumor potential doubling time T_p and the fraction of total dose delivered from the ^{125}I seeds. A sub-lethal damage repair half-life of 1.5 hr and a α/β of 10 for tumor were used in the calculation.

Figure 6 Biologically effective dose at 19 spatial locations along the 80 Gy prescription isodose line for the head and neck implant with ^{125}I and ^{103}Pd seeds for various tumor potential doubling times. A sub-lethal damage repair half-life of 1.5 hr and a α/β of 10 for tumor were used in the calculation.

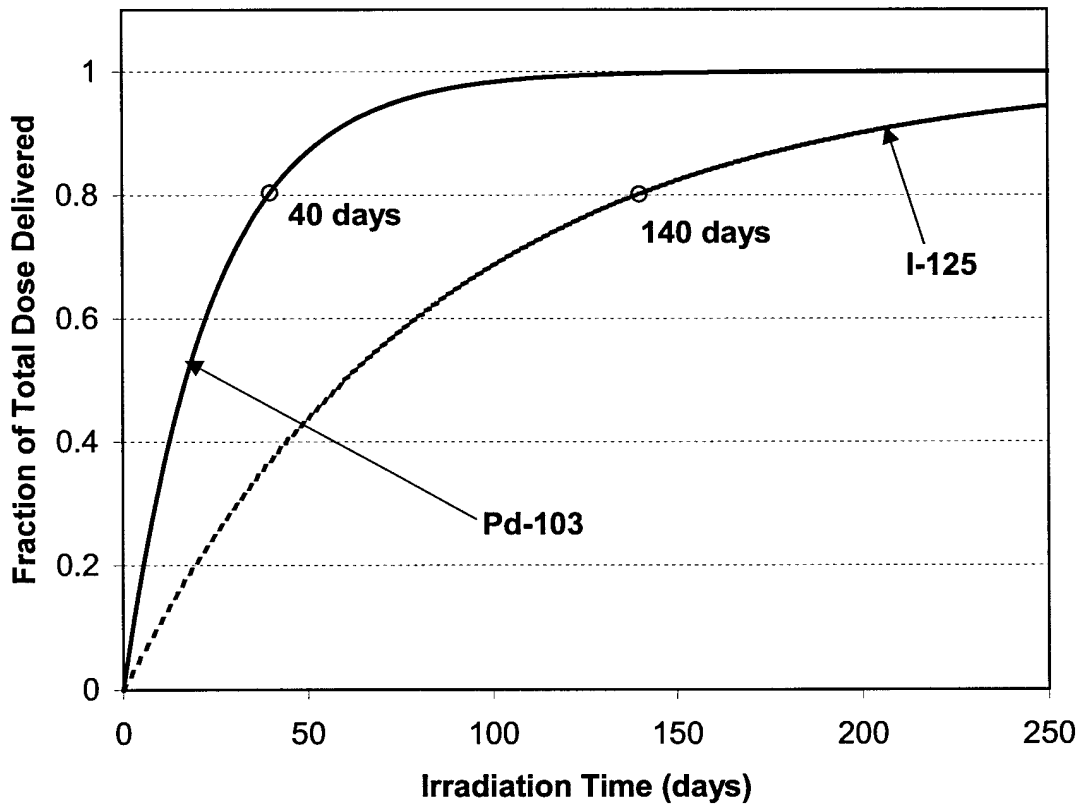
Fraction of Total Dose Delivered
1
0.8
0.6
0.4
0.2
0
0
50
100
150
200
250
Irradiation Time (days)
40 days
140 days
I-125
Pd-103

Figure 1

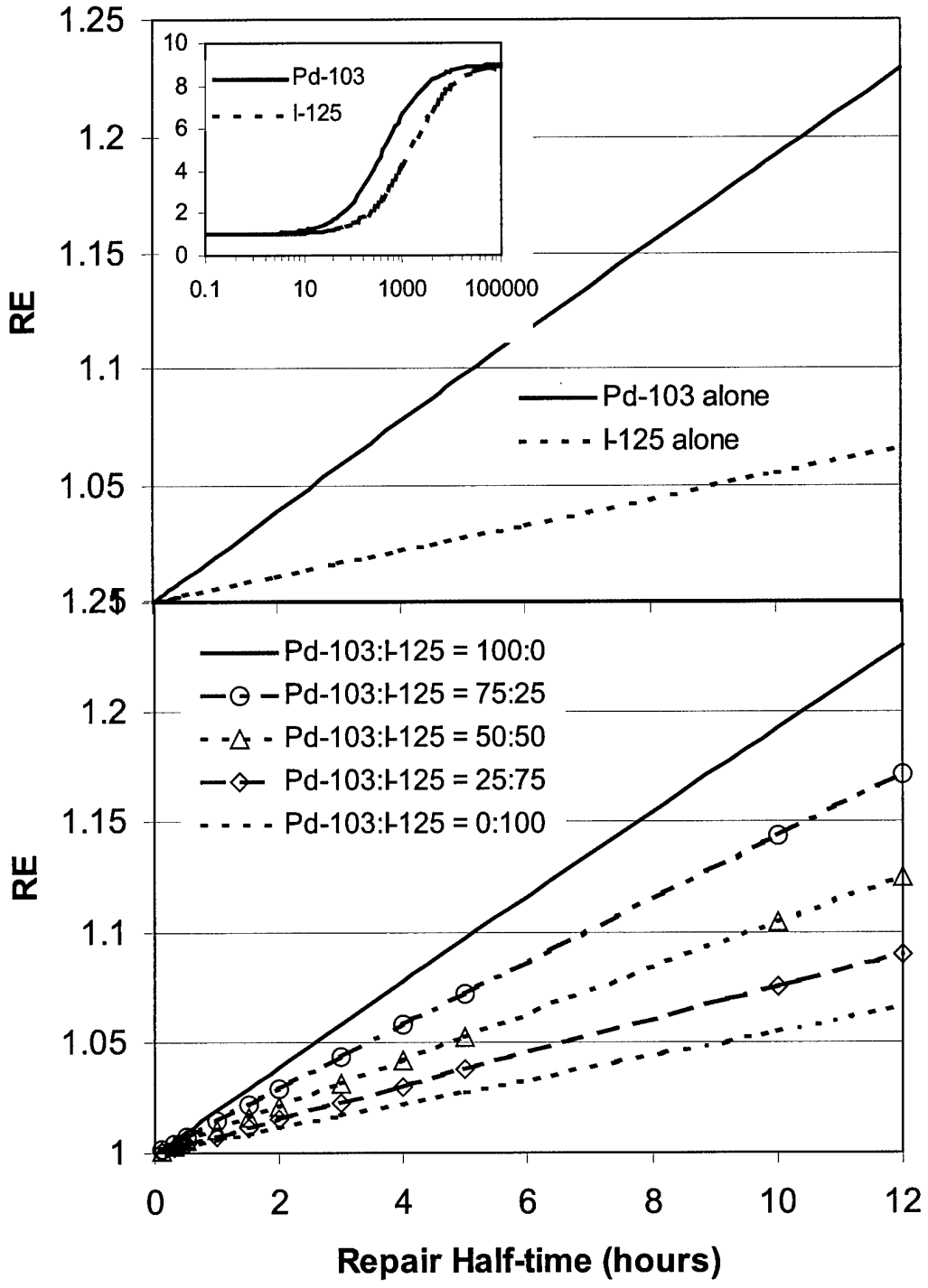
RE
1.25
1.2
1.15
1.1
1.05
1
10
8
6
4
2
0
0.1
10
1000
100000
Pd-103
I-125
Pd-103 alone
I-125 alone
Pd-103:I-125 = 100:0
Pd-103:I-125 = 75:25
Pd-103:I-125 = 50:50
Pd-103:I-125 = 25:75
Pd-103:I-125 = 0:100
0
2
4
6
8
10
12
Repair Half-time (hours)

Figure 2

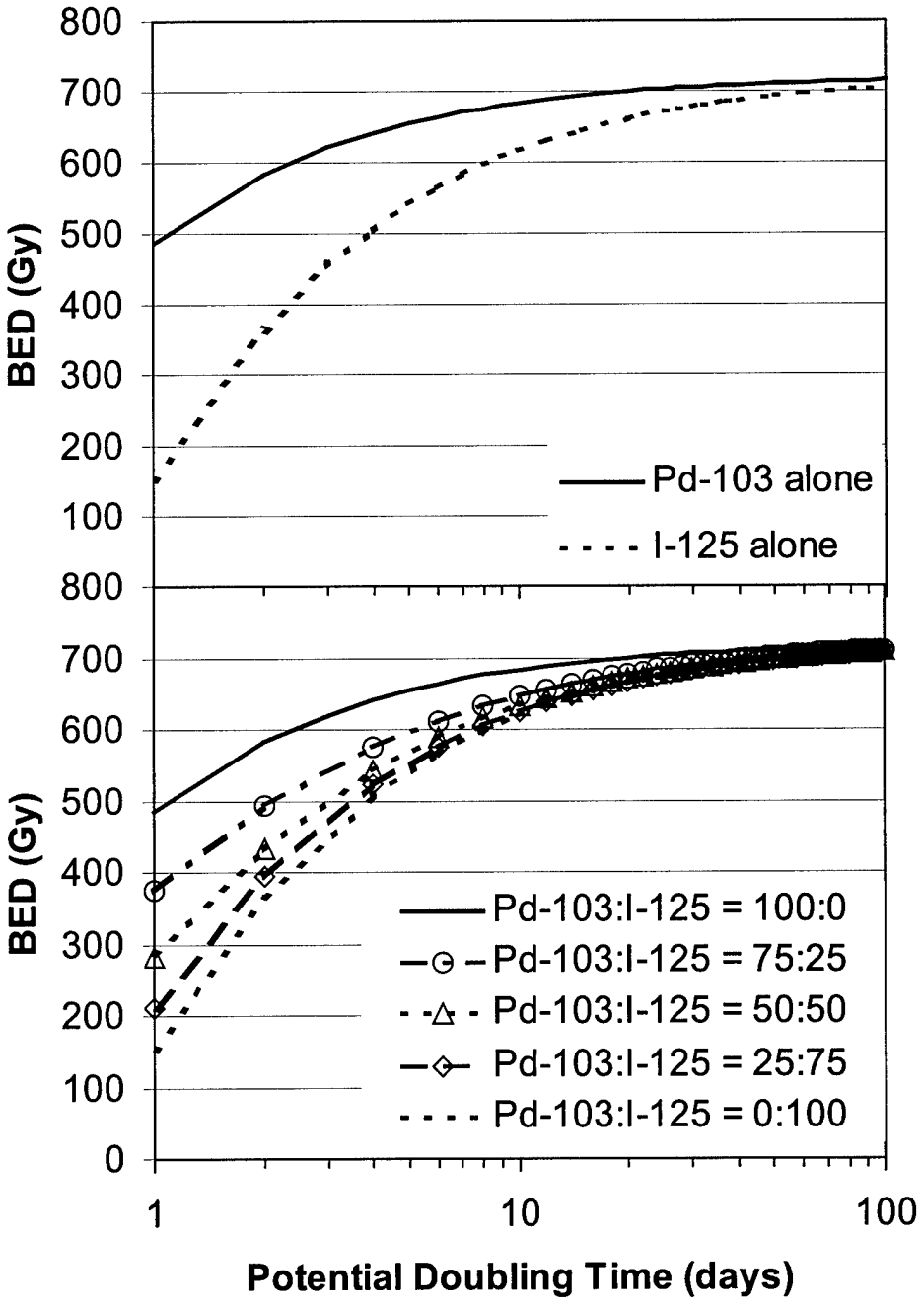
800
700
600
500
400
300
200
100
BED (Gy)
Pd-103 alone
I-125 alone
800
700
600
500
400
300
200
100
0
BED (Gy)
Pd-103:I-125 = 100:0
Pd-103:I-125 = 75:25
Pd-103:I-125 = 50:50
Pd-103:I-125 = 25:75
Pd-103:I-125 = 0:100
1
10
100
Potential Doubling Time (days)

Figure 3

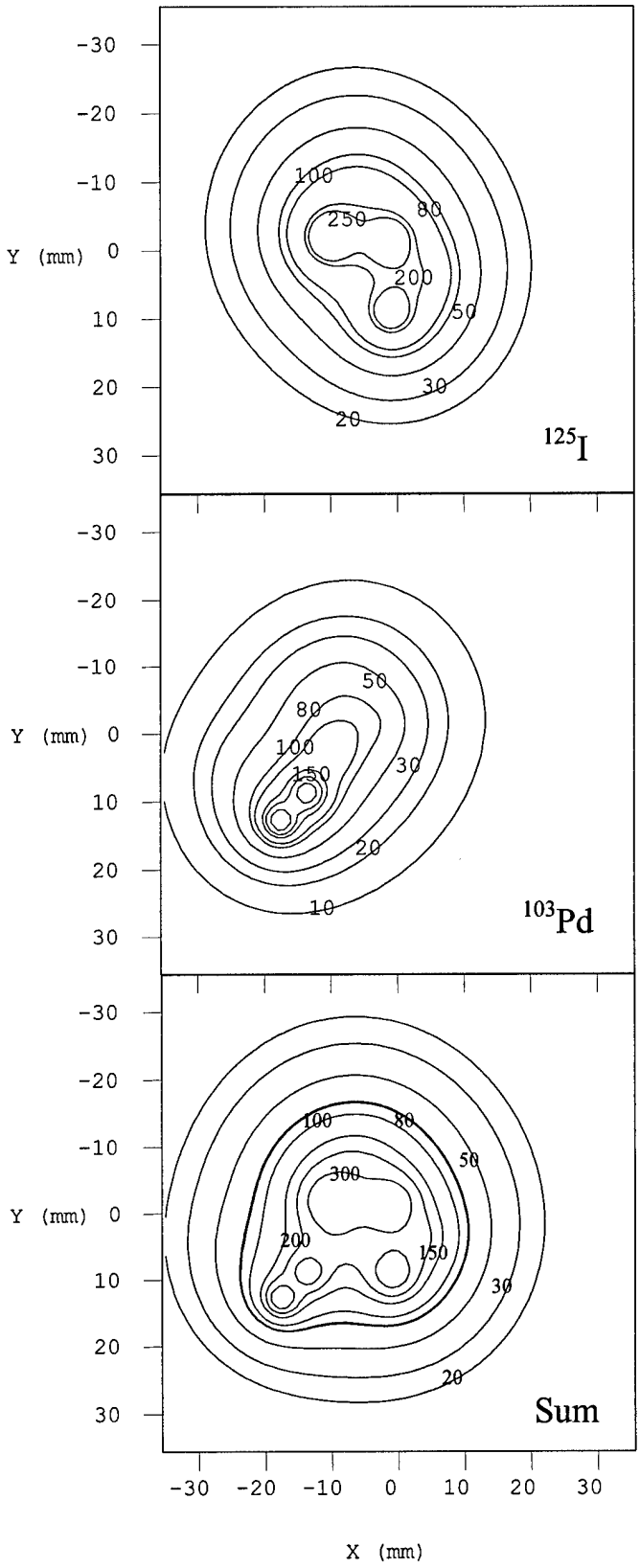
-30
-20
-10
Y (mm) 0
10
20
30
100
250
80
200
50
30
20
125I
-30
-20
-10
Y (mm) 0
10
20
30
50
80
100
150
30
20
10
103Pd
-30
-20
-10
Y (mm) 0
10
20
30
100
80
50
300
200
150
30
20
Sum
-30 -20 -10 0 10 20 30
X (mm)

Figure 4

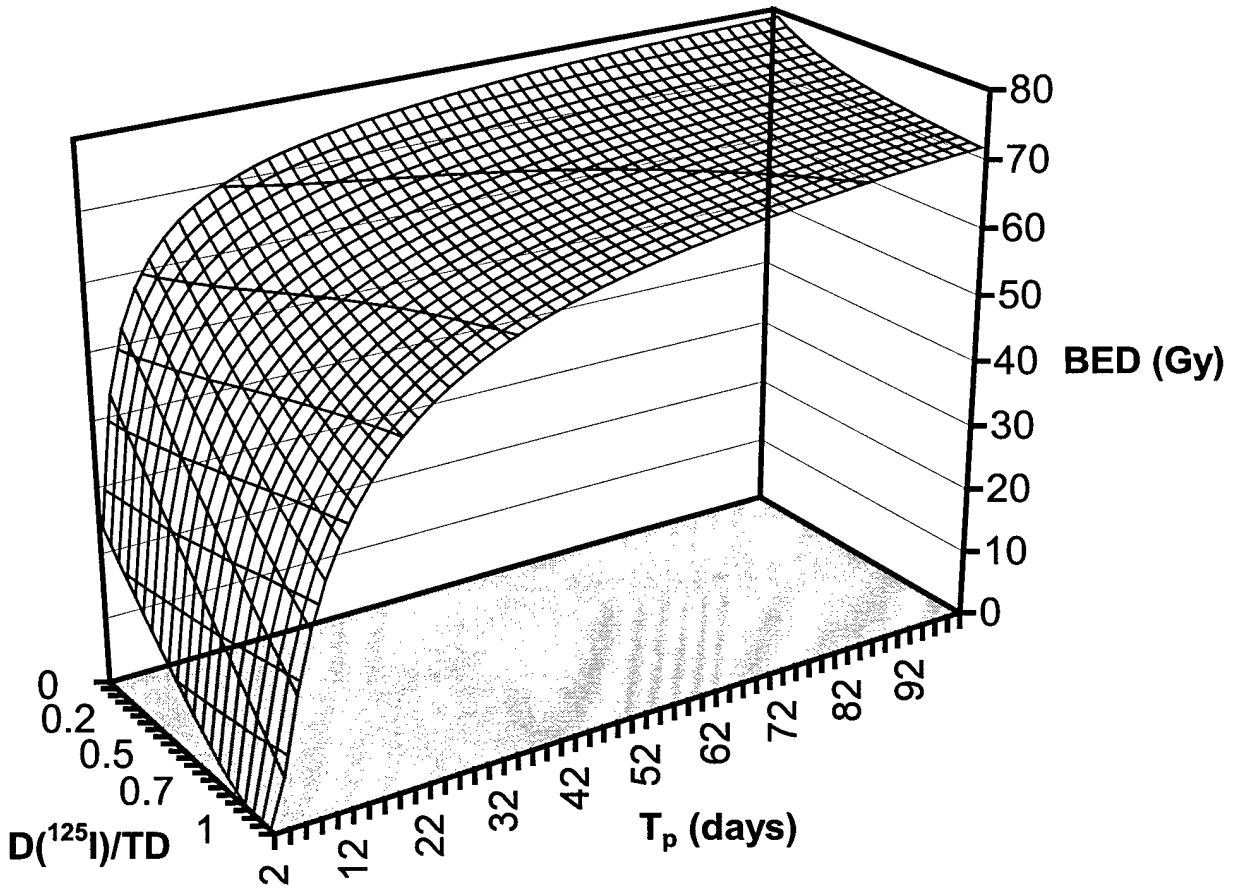
80
70
60
50
40
BED (Gy)
30
20
10
0
0
0.2
0.5
0.7
1
D(125I)/TD
2
12
22
32
42
52
62
72
82
92
Tp (days)

Figure 5

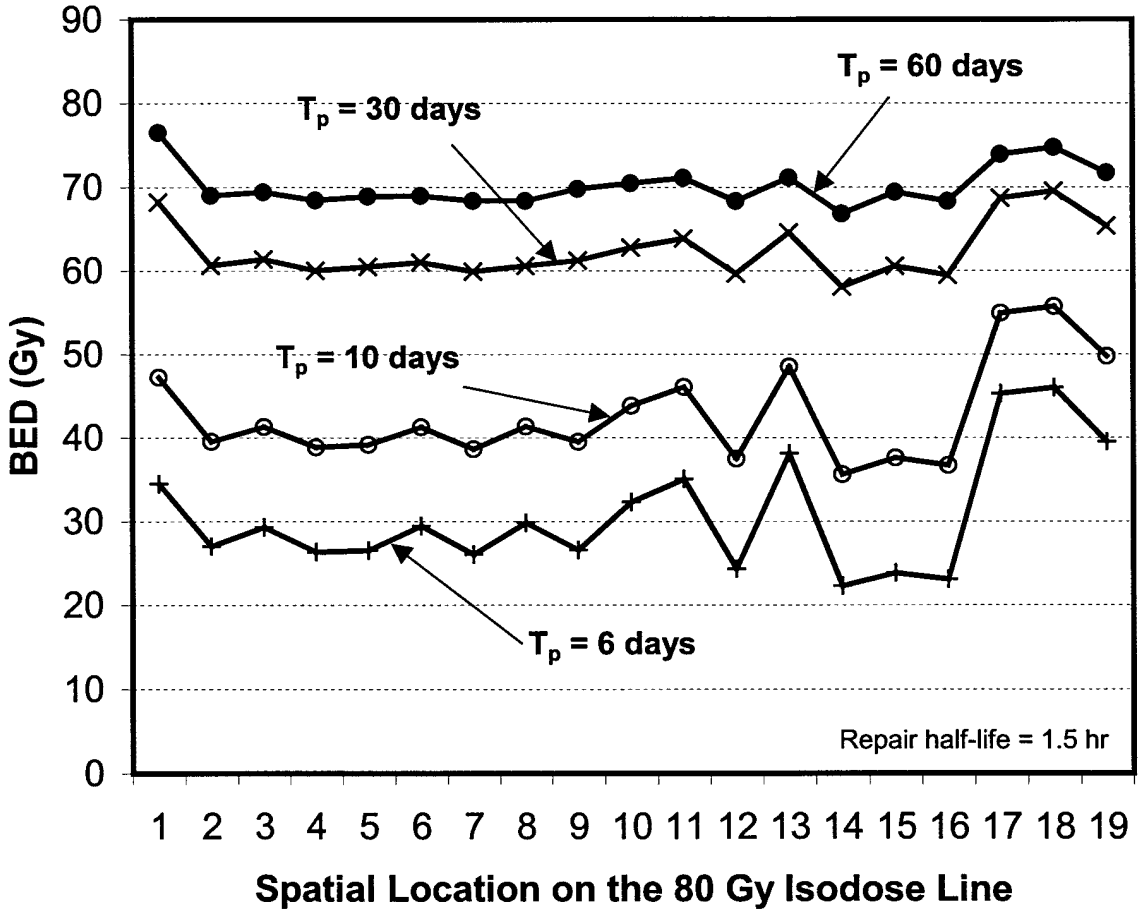
90
80
70
60
50
40
30
20
10
0
BED (Gy)
T_p = 60 days
T_p = 30 days
T_p = 10 days
T_p = 6 days
Repair half-life = 1.5 hr
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Spatial Location on the 80 Gy Isodose Line

Figure 6